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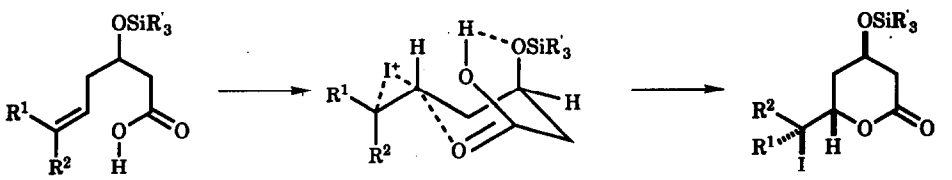
IODINE-INDUCED CYCLISATIONS OF (E)- AND (Z)-3-HYDROXY-5-ALKENOATES: STEREOSELECTIVE APPROACHES TO TRISUBSTITUTED TETRAHYDROFURANS

Frank Bennett,[a] Simon B. Bedford,[a] Kathryn E. Bell,[a] Garry Fenton,[b] David W. Knight [a,*] and Duncan Shaw[a]

[a] Department of Chemistry, University Park, Nottingham, NG7 2RD, UK.
[b]Rhone-Poulenc-Rorer, Central Research, Dagenham, Essex, RM10 7XS, UK.

Abstract:- *Iodoetherification of the (Z)-3-hydroxy-5-alkenoates* **4** *leads exclusively to the hydroxy-tetrahydrofurans* **5** *whereas similar cyclisations of the corresponding (E)-isomers [***10***,* **13** *and* **15***] give largely the iodo-tetrahydrofurans [***11***,* **14** *and* **16***].*

In the foregoing paper,[1] we report that iodine-induced cyclisations of 3-silyloxy-5-hexenoic acids **1** lead, somewhat unexpectedly,[2] to the *trans*-disubstituted valerolactones **3**, probably *via* a chair-like transition state **2** wherein the stereochemistry of the cyclisation is controlled by hydrogen bonding between the carboxylate function and the silyloxy group.

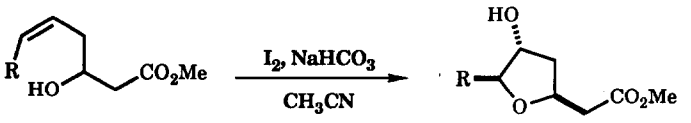


1 **2** **3**

During these studies, it was observed that very small quantities [> 5%] of byproducts were formed which appeared to be tetrahydrofurans; it seemed likely that these were formed by a 5-endo-trig process involving loss of the silyl group. In order to try and maximize such transformations, we have examined related cyclisations of the corresponding methyl 3-hydroxy-5-hexenoates. The methyl ester function was used as this was expected to prevent lactone formation while the free hydroxyl group should favour THF formation. Herein, we report the unexpected outcomes of such cyclisations.

When the methyl (Z)-3-hydroxy-5-alkenoate **4a** [1] was exposed to iodine [3 eq.] and sodium bicarbonate [3 eq.] in dry acetonitrile at -5 - 0°C for 60h, the *hydroxy*-tetrahydrofuran **5a** [2] was isolated, following

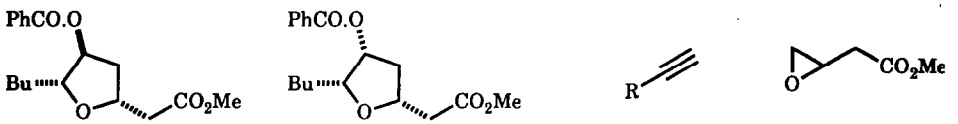
column chromatography, in 85% yield, accompanied by no more than traces of less polar 3-iodo-tetrahydrofurans. The cyclisation was relatively insensitive to the presence of water; from aqueous acetonitrile [1:1], the hydroxy-tetrahydrofuran **5a** was isolated in 70% yield. The corresponding 5-ethyl- and 5-phenethyl-hydroxy-tetrahydrofurans [**5b,c**] [2] were isolated in similar yields [87% and 70% respectively], in each case as single diastereoisomers. However, yields were much lower from cyclisations of the corresponding butyl and benzyl esters [*ca.* 30% and 10% respectively].



a) R = Bu
b) R = Et
c) R = $Ph(CH_2)_2$

4 **5**

The structures of these products were proven by the usual spectroscopic and analytical techniques, while the stereochemistry was determined largely by NOE studies. The assignment of stereochemistry was also consistent with those of a related series of trisubstituted 4-benzoyloxy-tetrahydrofurans, reported by Williams and his colleagues,[3] based upon chemical shift data. For this, we converted the initial product **5a** into the corresponding benzoate **6**,[2] [PhCOCl, py] and also into the epimeric benzoate **7** [2] by a Mitsunobu reaction [$PhCO_2H$, PPh_3, $EtO_2CN{=}NCO_2Et$].[4] Both esters exhibited spectral data in line with the Williams assignments, as well as appropriate NOE data.

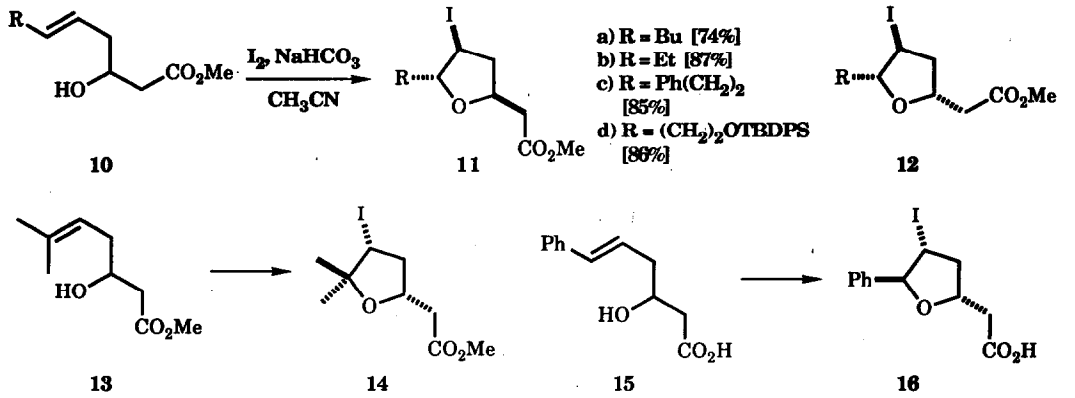


6 **7** **8** **9**

We next examined cyclisations of the corresponding (*E*)-3-hydroxy-5-alkenoates **10**, obtained by coupling the epoxy-ester **9** with vinylaluminium 'ate' complexes derived from the 1-alkynes **8**.[1] To our surprise, these underwent cyclisation under similar conditions [3 eq. I_2, 3 eq. $NaHCO_3$, CH_3CN] but more rapidly [<1h, 0°C] and lead instead to the iodo-tetrahydrofurans **11** [2] in excellent isolated yields. In each case, the cyclisations were highly stereoselective; each product was accompanied by <12% of a second epimeric iodo-tetrahydrofuran, the stereochemistry of which was established as the 2,5-*cis* epimers **12**, according to nOe measurements and coupling constant data.

The cyclisations of the *trans*-hydroxy-esters **10** were also relatively insensitive to the presence of water, although slightly better yields [5-10%] were realized when dry acetonitrile was used. These cyclisations are somewhat surprising as, in general, such electrophilic cyclisations of homoallylic alcohols

give very poor yields of tetrahydrofurans,[5] with the notable exception of phenylseleno-etherifications.[5,6] These types of cyclisation are formally unfavourable 5-*endo*-trig processes, which is consistent with the

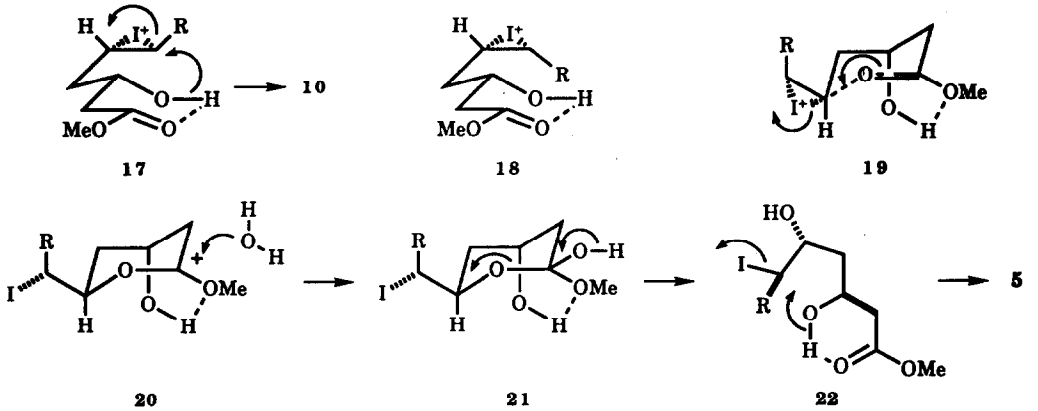


generally poor yields obtained. The cationic nature of the reactions however, means that they cannot really be considered as exceptions to Baldwin's rules.[7] Two further examples emphasize the cationic nature of such cyclisations. When the hydroxy-ester **13** was treated with iodine and bicarbonate in acetonitrile, only the *trans*-iodo-THF **14** [2] was isolated in 65% yield. When the hydroxy-acid **15** was reacted under the same conditions, the iodo-THF **16** [2] was formed, rather than the corresponding lactone.[8]

The highly stereoselective cyclisations of the *trans* hydroxy-alkenoates [**10**, **13** and **15**] can be explained by assuming the intermediacy of the transition state **17**. This features activation of the hydroxyl function with respect to cyclisation by hydrogen bonding with the ester group, in much the same way as the foregoing iodo-lactonisations were directed.[1] The insensitivity of such reactions to the presence of water is consistent with such an activation, the absence of which appears to allow hydration of the intermediate iodonium ion prior to cyclisation, leading to an iodohydrin.[5] The cyclisations of the hydroxy-ester **13** and especially the hydroxy-acid **15** to the corresponding iodo-THFs [**14** and **16**] are also consistent with this model as both of these substrates would be expected to produce particularly stable carbonium ions as the penultimate precursors to the tetrahydrofurans. In the latter case, the perhaps more expected iodolactonisation [1] would result in an electron deficient centre β- and not α-to the phenyl ring.

The cyclisations of the (Z)-isomers leading to the hydroxy-tetrahydrofurans are not so easily rationalized. Our initial idea that they arose *via* an S_N2 displacement of the corresponding all-*cis* iodo-THF were proven incorrect when a small sample of the latter was unchanged when exposed to the reaction conditions. In any event, this is an unlikely displacement as the electrophile can be regarded as a β-iodo-ether, which are well known to be relatively unreactive. Other likely intermediates, the epoxides derived from the alkenoates **4**, decomposed under the reaction conditions to a mixture which contained only traces of the hydroxy-THFs **5**. Therefore, we were lead to consider the involvement of the ester function in the

cyclisation. If it is assumed that the the transition state **18** is too crowded, then attack by the ester group on the iodonium function in conformation **19** would lead to the stabilized carbonium ion **20**. Trapping by water would then lead to the orthoester **21** and thence to iodo-diol **22**, cyclisation of which could again be assisted by intramolecular hydrogen bonding.[1] When a cyclisation of the (Z)-alkenoate **4a** was worked up after 3h, a compound corresponding [^{1}H NMR, ir] to the iodo-diol [**22**; R = Bu^n] was isolated admixed with the THF **5a**, which was completely converted into the latter upon exposure to only sodium bicarbonate in acetonitrile.



As the starting hydroxy-alkenoates **4** and **10** are available in optically active forms[1], the foregoing reactions should be applicable to the elaboration of chiral trisubstituted tetrahydrofurans; efforts to exploit and extend these in target synthesis are in progress.

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